

## REMARKS

Applicants submit this amendment in response to the Office Action dated February 11, 2004. Claims 1-37 are pending. Claims 3 and 14 are canceled herein. Claim 1 is amended herein to remove the amino acid substitution Gln to His. Claims 1-2, and 4-9 are under consideration, and no new matter is added.

Claims 1, 3-9 and 14 are rejected under 35 U.S.C. § 112, first paragraph as the specification allegedly lacks enablement for the full scope of the claims. The Examiner bases the rejection as the failure of the specification to “provide sufficient guidance as to which core structure of SEQ ID NO:4 is essential for maintaining its mitogenic activity and which changes can be made in the structure of SEQ ID NO:4 and still maintain the same function”. The applicants request reconsideration of this rejection on the following grounds. Several sections of the specification describe the criteria for making conservative amino acid substitutions, including page 15 lines 27-29 (continued on page 16 lines 1-13), page 19 lines 6-21, and page 20 lines 3-18. These passages recite that there are four families of amino acids; acidic, basic, non-polar, and uncharged polar. The family of non-polar amino acids further contains a sub-family that includes aromatic amino acids. Lines 6-21 on page 19 state that the replacement of an amino acid with a structurally related amino acid, such as an amino acid in the same family, will not have a major effect on the biological properties of the resulting variant. All of the amino acid substitutions listed in amended claim 1 are identified by family and satisfy the criteria specified on page 19 and therefore do not constitute grounds for a new matter rejection.

The Examiner asserts that the specification at page 11, lines 13-17 only discloses the “general method by which the applicant calculated a sequence identity or percent conservation or which of two residues represent a conservative amino acid substitution”. However, the applicants submit that the following other sections of the specification describe conservative amino acid changes relate to testing the mutated proteins in a functional assay:

Page 16 Lines 9-13: “Whether an amino acid change results in a functional protein or polypeptide can be readily determined by assaying biological properties of the disclosed proteins or polypeptides. For example, mitogenic biological properties can be measured by examining the effect of the protein or polypeptide’s expression on *Xenopus* oocyte maturation, as discussed in Example 3.”

Page 19 Lines 19-21: “It is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related

amino acid will not have a major effect on the biological properties of the resulting variant.”

The applicant asserts that in addition to disclosing conservative amino acid substitutions as they relate to calculations of overall sequence identity, the disclosed conservative amino acid changes relate directly to the function of the EGFH2 protein in the *Xenopus* oocyte maturation assay.

The biological assay is fully described in Example 3. In addition, Dr. Judith Abraham’s declaration of record February 26, 2003 provides further evidence that the biological activity of EGFH2 can be measured using proteins having a conservative amino acid substitution as described in the specification. Finally, conservative amino acid substitutes are well-known in the art. See, for example, Creighton (1984) Proteins, W.H. Freeman and Co.

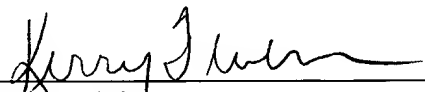
The Examiner states that “a description of a protein by functional language, i.e., having mitogenic activity as determined using *Xenopus* oocyte maturation assay in the absence of a structure is not considered sufficient to overcome 112 first rejection”. The applicants respectfully traverse this assertion and contend that the structure is provided in the specification, where conservative amino acid substitutions are clearly detailed in the above-mentioned sections.

For the foregoing reasons, reconsideration and withdrawal of the rejection are respectfully requested.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (206) 628-7650.

Respectfully submitted,  
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